FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2012/2013

Cristiano Martins Antunes

Lobectomy in follicular thyroid neoplasms' treatment

março, 2013

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UNIVERSIDADE DO PORTO

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Mestrado Integrado em Medicina

Área: Cirurgia Geral

Trabalho efetuado sob a Orientação de:
Doutor António Taveira Gomes

Trabalho organizado de acordo com as normas da revista:
Journal of Surgical Research

março, 2013

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Projeto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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Título da Dissertação:

Lobectomy in follicular thyroid neoplasms' treatment

Orientador:

Professor Doutor António Taveira Gomes

Ano de conclusão: 2013

Designação da área do projeto:

Cirurgia Geral

Faculdade de Medicina da Universidade do Porto, 19/03/2013

Assinatura: Cristiano Martins Antunes

Dedicatória

Ao meu orientador, Prof. Doutor António Taveira Gomes, e à Dra. Isabel Amendoeira

A ti Susana pelo apoio e carinho incondicional

À minha avó, mãe e irmão

Acima de tudo, ao meu pai.

Lobectomy in follicular thyroid neoplasms' treatment

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Categorization of manuscript - table of contents

Oncology/Endocrine

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Abstract

Background: The purpose of this study is to evaluate the suitability of lobectomy with isthmusectomy (LwI) in treatment of Follicular Thyroid Neoplasms (FTN), considering malignancy incidence and postoperative complications.

Methods: 192 patients (165 females; 27 males) who underwent LwI for FTN from 01/2005 to 12/2007 were retrospectively evaluated: clinical and pathological features, surgical complications and five year outcome of the remnant lobe. Inclusion criteria were cytological Bethesda category III and IV or histological follicular architecture. Patients with metastatic follicular carcinoma or previous thyroid surgery were excluded.

Results: Mean age was 48,68±14,93yrs. Overall malignancy occurred in 88 patients (45,83%) and 80 (41,67%) underwent thyroidectomy completion (TC), mainly by index lesion's malignancy. Forty-one (21,35%) in LwI and 31 (38,75%) in TC specimens had associated malignancy, mainly papillary microcarcinomas. High preoperative Thyroid-Stimulating Hormone (TSH), histological multinodularity and, in cytology category IV, younger age, were significantly associated to malignancy. Permanent recurrent laryngeal nerve lesion occurred in 0,58% in Lwl and 1,52% in TC, and temporary dysphonia occurred in 9,25% and 6,06% (LwI and TC respectively). No LwI patients presented hypoparathyroidism and 3,03% in TC had temporary symptoms. In LwI, 36,70% developed hypothyroidism. Higher preoperative TSH was associated with hypothyroidism development.

Conclusions: LwI was inappropriate in 40,10% patients with malignancy who required TC and 23,12% had no functional benefit because post-LwI hypothyroidism. Nodular relapse was reported in at least 23/113 LwI patients (20,35%). We propose total thyroidectomy for patients with FTN preoperative TSH higher than 2,16 mU/L and, in Bethesda category IV, less than 39,5yrs.

Key words: thyroid gland, thyroidectomy, follicular neoplasm, thyroid neoplasms, thyroid adenoma, Follicular Thyroid Carcinomas, complications, Fine-Needle Aspiration Biopsy, thyroid lobectomy, hemithyroidectomy.

Introduction

Thyroid differentiated cancer is the most common endocrine neoplasia and stands for 90% of thyroid cancers. Its incidence has increased in western world but its mortality has remained constant, suggesting a better diagnostic accuracy [1, 2]. Thyroid tumors present as nodular lesions which are highly prevalent. On physical examination, thyroid nodules are identified in 10% of patients and, by ultrasonography, there are reports of 67% [3]. However, only 5-30% of these are malignant [4]. With widespread use of Fine-Needle Aspiration Biopsy (FNAB), thyroid surgery for benign pathology has declined significantly. Despite a sensitivity of 83%, specificity of 92% and a accuracy of 95% [5], there is a "gray-zone" on FNAB which corresponds to Follicular Thyroid Neoplasms (FTN) whose uncertain nature requires histological evaluation [6]. FTN on FNAB can occur in nodular goiter, follicular adenoma (FA) as well as in well differentiated carcinomas (follicular carcinoma (FC) and follicular variant of papillary thyroid carcinoma (FVPTC)). The Bethesda System for reporting thyroid cytopathology has an implied risk of malignancy in category III of 5-15% and category IV of 15-30 % [7]. When FNAB revels a FTN, final diagnosis of FC depends on histological demonstration of capsular and/or vascular invasion; definitive diagnosis of FVPTC depends on a cytological evaluation with a better sample and/or histological diagnosis for nuclear atypia [8, 9]. Advances in molecular genetics have tried to define specific mutations for each FTN. RAS mutations and t(2,3) PAX8-PPAR-gama have been found in FTN however each mutation was found in the different FTN with similar frequencies [10, 11] and a study on genetic testing in indeterminate FNAB reported a sensitivity of 12%, specificity of 98%, a positive and negative predictive value of 38% and 65%, respectively [12]. So, despite several clinical, imaging and molecular features being associated with FTN nature, their role in therapeutic decision is yet limited, even when combined, which makes Lobectomy with Isthmusectomy (LwI) the most accurate diagnostic procedure. Preoperative characterization of FTN in a lesser invasive approach remains a challenge in endocrine pathology and a

significant controversy also remains in the definition of the best therapeutic approach [13, 14]. LwI is the minimal therapeutic procedure for patients with FTN, which has been accepted, since FTN are usually unifocal and malignancy risk is lesser than 30%. Patients who underwent LwI for FTN, had cancer in 19% and this procedure was considered adequate in 96% of patients [15], with comparable results to total thyroidectomy (TT) concerning recurrence and survival [16]. In more advanced neoplasms than T1N0M0, LwI had a 2,5-fold higher recurrence risk and 2,2-fold risk of death compared with TT [17], despite a lesser complications' rate [18, 19]. TT has a higher risk of permanent hypoparathyroidism and recurrent laryngeal nerve palsy and all patients develop hypothyroidism requiring lifelong opotheraphy. In LwI, opotheraphy will be required in at least 10,9% of patients, with 1 out of 25 patients developing clinical hypothyroidism [20, 21]. LwI can cure patients with FA and minimally invasive FC. It has minimal risk of hypoparathyroidism and a lower morbidity than TT. Patients with FC (widely invasive or angioinvasive) or FVPTC, ultimately will need a thyroidectomy completion (TC).

The aim of the present study is to evaluate the incidence of malignancy in patients with FTN who underwent LwI, morbidity of procedure, need for TC, late post-operative hypothyroidism and recurrent nodular disease.

Patients and methods

A retrospective study was carried out based on clinical files of patients who underwent LwI for FTN or follicular lesion of undetermined significance between January 2005 and December 2007 in Hospital de São João, Porto, Portugal, after approval by Ethical Commission Boarder. Inclusion criteria were lesions with cytological Bethesda category III and IV or histological FTN (FA, FC, FVPTC), independently of FNAB cytology. Patients with metastatic FC or previous thyroid surgery were excluded. All surgeries were performed in our center. FNAB diagnosis was made in our center and outside. The clinical, FNAB,

surgical and pathological reports and follow-up during 5yrs after surgery were analyzed. The clinical data evaluated were age, gender, cervical palpable mass and its location, symptoms of cervical compression (hoarseness, dysphagia, dyspneia and cervical discomfort), thyrotoxicosis and familial history of thyroid malignancy. FNAB were reclassified according to thyroid cytopathology Bethesda System. Surgical data included LwI specimen weight and surgical complications (definitive recurrent laryngeal nerve lesion, temporary dysphonia, hypoparathyroidism, hematoma/hemorrhage, abscess formation and keloid scar). Hypothyroidism in LwI group during 5yrs follow-up was also considered a complication. We also evaluated the reasons for TC. TC weight was recorded and complications were analyzed as previously mentioned to LwI patients. Pathological features review focused on macroscopic aspect (capsulated or non-capsulated), size, uni or multinodular disease, the main histological diagnosis and associated lesions, the histological FC invasiveness and angio-invasiveness, tumor margins and thyroiditis. Outcome at five years after surgery included: thyroid nodular relapse, hypothyroidism in LwI group, recurrence of malignant pathology (locally or at distance), and death related to thyroid pathology.

Statistical analysis

In few patients' records there was missing information about some of the cited topics, so obtained percentages have as denominator the population with valid information. Continuous variables with normal distribution were expressed in means with standard deviation and were compared through independent t-Student test. Those that had not a normal distribution were expressed in medians with interquartile ranges (IQR) and were compared with Mann-Whitney U-test. Categorical variables were presented as frequency and percentage. They were compared through a Pearson chi-square test or Fisher exact test. A p value $\leq 0,05$ was considered significant. ROC curves were employed to define the best sensitivity and specificity cutoff points concerning age and Thyroid-Stimulating Hormone (TSH) as predictors of malignancy (it was intended a cutoff point with a specificity of at least 80%). All

statistical analyses were obtained through Statistical Package for Social Science, version 20.0 (SPSS® IBM Corporation).

Results

A total of 192 patients were included in this study, 165 females (85,94%) and 27 males (14,06%). The mean age at diagnosis was 48,61 years ± 14,93 (range 14-80). Nodule occurred on the right lobe in 57,37% patients, and was palpable 76,87%. Compressive symptoms were reported in 33,65% patients. LwI median weight was 13,00g (IQR 12,00g, range 3,50-111,00g). A histological solitary nodule was reported in 118 patients (61,46%) while 74 (38,54%) had multiple nodular lesions. Nodule size was not registered in 4 patients. The remaining 188 patients had a median histological nodule size of 1,70 cm (IQR 1,70 cm); 33 patients (17,55%) had an less than 1 centimeter nodule, 71 patients (37,77%) with 1-1,9 cm nodule, 60 patients (31,91%) 2-3,9cm nodule and in 24 (12,77%) being ≥ 4 cm.

All patients underwent LwI and 80 (41,67%) required a TC with median time to completion surgery being 96 days (IQR 52; range 15-1434). TC were required by index lesion's malignancy (77 patients [40,10%]), a benign index lesion associated malignant diagnosis (2 patients [1,04%]) and by nodular benign relapse in 1 patient (0,52%) with benign index lesion. TC weight median was 7,15g (IQR 4,00g, range 1,00-24,00g). Pathological analysis is explained on *table 1*. Excluding microcarcinomas, 75 (39,06%) of index lesions were malignant. Surgical margins in malignant lesions were classified as R0 in 68 out of 73 patients (93,15%) and R1 in 5 (6,85%). Vascular invasion was found in 12 out of 75 carcinomas (16,00%). All patients with R1 borders and/or vascular invasion underwent TC. Thyroiditis identified was in 97 out of 180 patients (53,89%). Histological evaluation from TC specimen was "normal" in 19 patients (23,75%), benign in 30 (37,50%) and malignant in 31 (38,75%) – 22 (27,50%) being microcarcinomas. In the 192 patients, concerning other diagnosis besides index lesion in LwI and TC specimens, 48 (25,00%) presented an incidental

papillary microcarcinomas (30 in LwI and 22 in TC specimen – in 4 patients it was detected in LwI and in TC specimens). TSH pre-surgical value was higher in patients with malignant diagnosis (median in malignant 1,50, IQR 0,10; median in benign 1,30, IQR 1,19; p=0,027), with malignancy being less frequent in patients with thyrotoxicosis (p=0,015). Histological multinodular pathology was significantly associated with malignancy (p=0,001). It was not found a statistical significant difference concerning all others clinical and pathological features evaluated. Patients FNAB re-classification is listed on *table 2*. Excluding microcarcinomas in index nodule, 23,08% from Bethesda category III and 33,33% from category IV were malignant. There was not a significant difference between Bethesda categories III or IV and malignancy. In patients with Bethesda category IV, a malignant diagnosis was more frequent at lower age (mean benign 51,81 yrs ±13,66; mean malign 44,72 yrs ± 15,92; p=0,016) and higher pre-operative TSH (median in benign 1,19, IQR 0,86; median in malign 1,56, IQR 1,45; p=0,045). No statistical significant difference was found regarding all others clinical and pathological features evaluated. In patients with Bethesda category III, older age was associated with malignancy (mean benign 44,94 yrs ± 11,03; mean malign 61,78 yrs ± 12,43; p=0,002). No statistical significant difference was found concerning all others clinical and pathological features evaluated.

An TSH pre-operatory value higher than 2,16 mU/L (sensitivity 28,60%; specificity 79,7%; Area Under the Curve [AUC] 0,615, 95% Confidence Interval [CI95%]: 0,52-0,71) and, in Bethesda category IV, age lesser than 39,5yrs (sensitivity 37,20%; specificity 79,00%; AUC 0,63; CI95%: 0,26-0,48) were associated with a malignant diagnosis.

Surgical complications are listed on *table 3*. Isolated LwI immediate complications occurred in 19 patients; late onset complications during follow-up (keloid scar and hypothyroidism) occurred in 38 patients and 3 patients had both immediate and late onset complications (hypothyroidism). A nodular relapse in LwI group was observed in 22 LwI group patients (56,41%) out of 39 who, despite a benign diagnosis, were followed in our center. One additional patient required TC by benign relapse during follow-up. In LwI group, 40 patients

(36,70%) out of 109 patients developed hypothyroidism, with higher pre-operatory TSH value (p=0,011) being associated to a higher post-operatory hypothyroidism risk. No malignant thyroid disease relapse was notified in any patient nor death for thyroidal disease.

Discussion

FTN malignancy rate has been reported to be lesser than 30% [7], however preoperative identification and surgical management remain controversial. Globally, we found a higher malignancy rate of 45,83%. Excluding incidental microcarcinomas, FNAB III and IV categories presented values slightly higher (23,08% and 33,33% respectively) than those predicted according to thyroid cytopathology Bethesda system [7]. Other studies have also found higher malignancy frequencies. Baloch ZW *et al.* found 31% malignancy rate in 122 patients who underwent thyroid surgery for FTN [6] and Kim ES found a malignancy rate, in 215 patients, of 47,9% [22]. We verified that incidental microcarcinomas were prevalent (25% of patients). Despite papillary microcarcinomas not being an indication to TT, since they are indolent and 99% are cured by LwI, rarely their presentation is a metastasis [23]. Several malignancy associated risk factors have been described, including younger age, male gender, larger nodule size, ultrasonography characteristics and higher tireoglobuline levels [24-28]. Nonetheless, this has not being uniformly reported in all studies. In our series, only higher TSH values, no thyrotoxicosis, histological multinodularity and, in Bethesda IV, lower age were associated with malignancy.

Spanheimer PM *et al.* found that 18,81% patients who underwent thyroid LwI required completion surgery and that 42,2% required opotheraphy [29], so, in this series, LwI could be considered as an inappropriate approach or without functional benefits in 61,01% of patients. In our study, TC was required in a high proportion of patients (41,67%), mainly by malignant disease in index nodule or as associated lesions. Besides, in LwI group, 35,78% patients presented hypothyroidism during follow-up, which corresponds to 23,12% from initial

population whose complications were registered. So, we can consider that LwI was inappropriate or without functional benefit in 64,79% of patients which may support a more extensive approach such as TT. Additionally, we observed a nodular relapse of at least 20,35% (23/113) during 5 year follow-up period, and if all patients had been followed, a higher rate would be expected. In our experience (unpublished data) nodular relapse will occur in almost all patients until 30 years after initial diagnosis which could justify follow-up for all patients, including those with benign diagnosis. Yet, despite this high rate of nodular relapse, most patients will not need TC.

Rosato *et al.* followed 14934 patients during 5 years and concluded that LwI is the safest thyroidal surgery with a lower morbidity when compared with TT [30]. We found similar rates in LwI complications as Rosato, except temporary dysphonia which was higher in our series. Despite LwI being the safest surgical procedure, we found a high TC requirement rate and a relatively low morbidity increment. Vaiman *et al.* verified that, in multinodular goiter, complications occurrence rate was higher when LwI were combined with completion surgery versus LwI only, but no statistical significant difference in complications occurrence among TT and lesser invasive approaches [31].

In summary, high rate of malignancy and completion surgery requirement were observed in our patients with FTN as long as post-LwI hypothyroidism which made LwI inappropriate or without functional benefit in a significant amount of patients. Additionally, LwI is associated to a higher economical burden in management the remnant lobe and complications occurrence is not different between this approach and TT. We propose total thyroidectomy as the initial approach for patients with FTN with preoperative TSH higher than 2,16 mU/L and, in Bethesda category IV, less than 39,5yrs. More studies are required to find preoperative criteria to identify malignancy on FTN. The increase of preoperative sensitivity, reducing second surgery need, depends on the selection of the nodule(s) to be biopsied, expertise of cytopathologists and, hopefully, the introduction of new molecular studies in routine clinical practice.

References

1. Mazeh H, Chen H. Advances in surgical therapy for thyroid cancer. Nat Rev Endocrinol 2011;7:581.

2. Borson-Chazot F, Bournaud C. Thyroid cancer screening: is it useful? Presse Med 2011;40:1182.

3. Langer JE, Baloch ZW, McGrath C, Loevner LA, Mandel SJ. Thyroid nodule fine-needle aspiration. Semin Ultrasound CT MR 2012;33:158.

4. Granados-Garcia M, Cortes-Flores AO, del Carmen Gonzalez-Ramirez I, Cano-Valdez AM, Flores-Hernandez L, Aguilar-Ponce JL. Follicular neoplasms of the thyroid: importance of clinical and cytological correlation. Cir Cir 2010;78:473.

5. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations, and effect. Mayo Clin Proc 1994;69:44.

6. Baloch ZW, Fleisher S, LiVolsi VA, Gupta PK. Diagnosis of "follicular neoplasm": a gray zone in thyroid fine-needle aspiration cytology. Diagn Cytopathol 2002;26:41.

7. Cibas ES, Ali SZ. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol 2009;132:658.

8. Wang TS, Roman SA, Sosa JA. Management of follicular tumors of the thyroid. Minerva Chir 2007;62:373.

9. Sobrinho-Simoes M, Eloy C, Magalhaes J, Lobo C, Amaro T. Follicular thyroid carcinoma. Mod Pathol 2011;24 Suppl 2:S10.

10. Bhaijee F, Nikiforov YE. Molecular analysis of thyroid tumors. Endocr Pathol 2011;22:126.

11. Castro P, Rebocho AP, Soares RJ, et al. PAX8-PPARgamma rearrangement is frequently detected in the follicular variant of papillary thyroid carcinoma. J Clin Endocrinol Metab 2006;91:213.

12. Moses W, Weng J, Sansano I, et al. Molecular testing for somatic mutations improves the accuracy of thyroid fine-needle aspiration biopsy. World J Surg 2010;34:2589.

13. Smith J, Cheifetz RE, Schneidereit N, Berean K, Thomson T. Can cytology accurately predict benign follicular nodules? Am J Surg 2005;189:592.

14. Castro MR, Gharib H. Continuing controversies in the management of thyroid nodules. Ann Intern Med 2005;142:926.

15. Wiseman SM, Baliski C, Irvine R, et al. Hemithyroidectomy: the optimal initial surgical approach for individuals undergoing surgery for a cytological diagnosis of follicular neoplasm. Ann Surg Oncol 2006;13:425.

16. Shah JP, Loree TR, Dharker D, Strong EW. Lobectomy versus total thyroidectomy for differentiated carcinoma of the thyroid: a matched-pair analysis. Am J Surg 1993;166:331.

17. Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. J Clin Endocrinol Metab 1997;82:3553.

18. Friedman M, Pacella BL, Jr. Total versus subtotal thyroidectomy. Arguments, approaches, and recommendations. Otolaryngol Clin North Am 1990;23:413.

19. Vaiman M, Nagibin A, Hagag P, Buyankin A, Olevson J, Shlamkovich N. Subtotal and near total versus total thyroidectomy for the management of multinodular goiter. World J Surg 2008;32:1546.

20. Su SY, Grodski S, Serpell JW. Hypothyroidism following hemithyroidectomy: a retrospective review. Ann Surg 2009;250:991.

21. Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 2012;97:2243.

22. Kim ES, Nam-Goong IS, Gong G, Hong SJ, Kim WB, Shong YK. Postoperative findings and risk for malignancy in thyroid nodules with cytological diagnosis of the so-called "follicular neoplasm". Korean J Intern Med 2003;18:94.

23. Baloch ZW, LiVolsi VA. Microcarcinoma of the thyroid. Adv Anat Pathol 2006;13:69.

24. Schlinkert RT, van Heerden JA, Goellner JR, et al. Factors that predict malignant thyroid lesions when fine-needle aspiration is "suspicious for follicular neoplasm". Mayo Clin Proc 1997;72:913.

25. Lee EK, Chung KW, Min HS, et al. Preoperative serum thyroglobulin as a useful predictive marker to differentiate follicular thyroid cancer from benign nodules in indeterminate nodules. J Korean Med Sci 2012;27:1014.

26. Tuttle RM, Lemar H, Burch HB. Clinical features associated with an increased risk of thyroid malignancy in patients with follicular neoplasia by fine-needle aspiration. Thyroid 1998;8:377.

27. Gulcelik NE, Gulcelik MA, Kuru B. Risk of malignancy in patients with follicular neoplasm: predictive value of clinical and ultrasonographic features. Arch Otolaryngol Head Neck Surg 2008;134:1312.

28. Besic N, Sesek M, Peric B, Zgajnar J, Hocevar M. Predictive factors of carcinoma in 327 patients with follicular neoplasm of the thyroid. Med Sci Monit 2008;14:CR459.

29. Spanheimer PM, Sugg SL, Lal G, Howe JR, Weigel RJ. Surveillance and intervention after thyroid lobectomy. Ann Surg Oncol 2011;18:1729.

30. Rosato L, Avenia N, Bernante P, et al. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg 2004;28:271.

31. Vaiman M, Nagibin A, Olevson J. Complications in primary and completed thyroidectomy. Surg Today 2010;40:114.

Table 1 – Pathological diagnosis

LwI – Main histological diagnosis	Index nodule	Associated lesions	Completion thyroidectomy[a]
	n (%)	n (%)	n/N (%)
Benign[b]	102 (53,13%)	36 (18,75%)	3/102 (2,94%)[c]
WDTUMP[d]	2 (1,04%)	-	0/2 (0%)
Malign	88 (45,83%)	41 (21,35%)	77/88 (87,5%)
Follicular carcinoma	3 (1,56%)	-	3/3 (100%)
Minimally invasive	1		
Widely invasive	0		
Angio-invasive	2		
Hurthle cell follicular carcinoma	3 (1,56%)	-	3/3 (100%)
Minimally invasive	0		
Widely invasive	0		
Angio-invasive	3		
Follicular variant papillary carcinoma	40 (20,83%)	6 (3,125%)	38/40 (95,00%)[e]
Papillary carcinoma Hurthle cell variant	27 (14,07%)	3 (1,56%)	27/27 (100%)
Classic papillary carcinoma	1 (0,52%)	2 (1,04%)	1/1 (100%)
WDCNOS[f]	1 (0,52%)	-	1/1 (100%)
MicroFVPTC	12 (6,25%)	-	4/12 (33,33%)
Micro PTC Hurthle cells variant	1 (0,52%)	-	0/1 (0,00%)
Papillary microcarcinoma	-	30 (15,625%)	-
Normal	-	115 (59,90%)	-

a) According to index nodule histological diagnosis.

b) Benign diagnosis – FA, FA with Hurthle cells, Hurthle cells adenoma, colloid nodule and Hashimoto thyroiditis.

c) In 2 patients, TC was required by malignant associated lesion.

d)Well Differentiated Tumor of Uncertain Malignant Potential

e) One patient who did not underwent TC surgery had a FVPTC with 1,10 cm and associated benign adenomatous nodules. The other one had a solitary FVPTC with 1,00 cm.

f) Well Differentiated Carcinoma Non Otherwise Specified.

Table 2 – Cytological diagnosis (Bethesda Classification System for thyroid cytopathology)

FNAB [a]	N (%)	Malignancy in histology N(%)
I	9 (4,79%)	-
II	25 (13,30%)	-
III	26 (13,83%)	9 (34,61%)
IV	105 (55,85%)	43 (40,95%)
V	23 (12,23%)	-
Total	188 [b]	

a) Reclassification based on Bethesda classification system (FNAB I, II and V were included because histological exam revealed a FTN).

b) In four patients FNAB was unknown.

Table 3 - Surgical complications

LwI complications[a]		TC complications[b]	
Permanent RLN[c] lesion	1 (0,58%)	Permanent RLN lesion	1 (1,52%)
Temporary dysphonia	16 (9,25%)	Temporary dysphonia	4 (6,06%)
Hematoma/Hemorrhage	4 (2,31%)	Temporary hypoparathyroidism	2 (3,03%)
Abscess	1 (0,58%)	No	59 (89,39%)
Hypertrophic or keloid scar	2 (1,16%)		
Hypothyroidism	40 (23,12%)[d]		
No	113 (65,32%)		

a) Unknown in 19 patients.

b) Unknown in 14 patients.

c) RLN - Recurrent Laryngeal Nerve

d) Isolated hypothyroidism occurred in 36 (20,81%) patients and 4 patients had another associated LwI complication (3 an acute and in 1 a late onset complication).

Anexos

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When reporting experiments on human subjects indicate whether the procedures followed were in accordance with the ethical standards of the committee on human experimentation of the institution in which the experiments were done or in accordance with the Helsinki Declaration of 1975. When reporting experiments on animal subjects indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

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1. Bellows CF, Jaffe BM. Glutamine is essential for nitric oxide synthesis by marine macrophages. J Surg Res 1999;86:213.

2. Thakur A, Thakur V, Fonkalsrud EW, Singh S, Buchmiller TL. The outcome of research training during surgical residency. J Surg Res 2005 (in press).

3. Sommer A. Nutritional blindness: Xerophthalmia and keratomalacia. New York: Oxford University Press, 1982.

4. Svanes K, Critchlow J, Takeuchi K, et al. Factors influencing reconstitution of frog gastric mucosa. In: Allen A, Flemstrom G, Garner A, Silen W, and Turnberg LA, eds. Mechanisms of mucosal protection in the upper gastrointestinal tract. New York: Raven Press, 1984:33-39.

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Updated April 2012

Comissão de Ética para a Saúde do Centro Hospitalar de São João/
Faculdade de Medicina da Universidade do Porto
Porto - Portugal

CES

Ethics Reference No:	**35/2013**
Project Title:	**Lobectomy in follicular thyroid neoplasms' treatment**
Researcher Name:	**António Taveira Gomes, PhD, Cristiano Martins Antunes**

The Ethics Committee for the Health (Comissão de Ética para a Saúde - CES) had approved this study from an ethical point of view on 25-01-2013.

Yours sincerely

15-03-2013

The Secretary of Ethics Committee for the Health

PhD Pedro Brito

CES 35-13

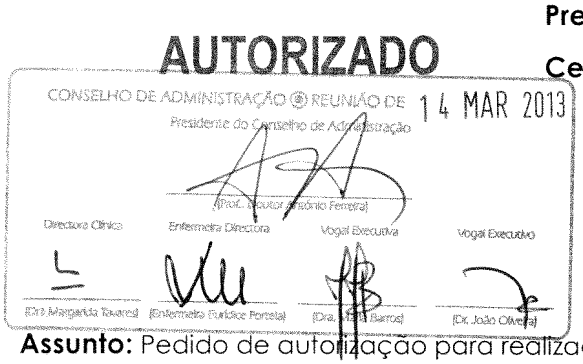
No CA e para
parecer da DC

7.3.2013

Exmo. Senhor

Presidente do Conselho de Administração do

Centro Hospitalar de S. João – EPE



Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: António Tarcísio Gomes

Título do projecto de investigação: A laparotomia no tratamento das neoplasias foliculares da tiroide

Pretendendo realizar no(s) Serviço(s) de Cirurgia Geral do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 5 Dezembro / 2012

O INVESTIGADOR/PROMOTOR

Comissão de Ética para a Saúde – Centro Hospitalar São João

Parecer

Título do Projecto: A Lobectomia no Tratamento das Neoplasias Foliculares da Tireóide.

Nome do Investigador Principal: Prof. Doutor António Taveira Gomes.

Local onde sera realizado o estudo: Serviço de Cirurgia Geral – CHSJ, havendo autorização do respectivo Diretor de Serviço para a realização do mesmo.

Objectivo do estudo: Trata-se de um estudo observational e retrospetivo. Os objetivos do estudo são: avaliar as características dos doentes submetidos a lobectomia; determinar o número de casos em que há malignidade e o estado funcional pós lobectomia nos casos de benignidade; avaliar as complicações associadas com este procedimento e o prognóstico 5 anos após a cirurgia;

Período previsto de conclusão: Março 2013

Benefício / Risco: Não existem benefícios imediatos, nem riscos para os doentes.

Respeito pela liberdade e autonomia do sujeito do ensaio: N/A

Confidencialidade dos dados: está garantida a confidencialidade dos dados e esta informação será restrita ao investigador principal.

O Investigador Principal dispõe de competência técnica e científica para a realização do estudo.

Não prevê a realização de questionário.

Custos: O estudo não prevê custos acrescidos para a instituição.

Parecer: Em face da análise do protocolo de estudo, proponho a sua aprovação pela CES do CHSJ.

Porto, CHSJ, 22 de janeiro de 2013

O Relator

Dr. John Preto

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)

NÃO ☐

NÃO APLICÁVEL ☑

8. TERMO DE RESPONSABILIDADE

Eu, António Taveira Gomes,

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 5 / 12 / 2012

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 25 / Janeiro / 2013

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Apêndices

Cristiano Martins Antunes

Medicine Faculty of University of Porto
Surgical department of Hospital de São João
Alameda Professor Hernâni Monteiro,
4200-319 Porto, Portugal

Editorial Board, Journal of Surgical Research

Porto, March 11, 2013

Dear Sir or Madam

A thyroid cytology presenting a follicular thyroid neoplasm remains a challenge to surgeon decision making. First, because it remains impossible to define the character benign versus malignant without histological analysis. In the other hand, despite lobectomy with isthmusectomy has potential to be curative, we do not know what patients would benefit from a more extensive approach as total thyroidectomy.
As you shall see, 192 patients submitted to lobectomy with isthmusectomy during three consecutive years were studied concerning final histological diagnosis, post-lobectomy hypothyroidism and surgical complications occurrence in our center.

Basically, lobectomy was inappropriate in 41,67% patients who required thyroidectomy completion, mainly by a malignant diagnosis. It was also verified that, in patients submitted to lobectomy, 23,12% had no functional benefit because post-surgical hypothyroidism and a nodular relapse in the 5yrs after surgery occurred in at least patients 20,35%. Concerning our data, and trough ROC curves, we verified that TSH higher than 2,16 mU/L and, in Bethesda category IV, less than 39,5yrs (with a specificity close to 80%) were associated with a malignant diagnosis and perhaps these patients would benefit from a total thyroidectomy as initial approach.

The present study was elaborated in my dissertation Master Degree in Medicine by Medicine Faculty of University of Porto. There are not any conflicts of interest to report and no entity sponsored this study.

Yours faithfully, with best regards

Cristiano Antunes